TRANSDERMAL PATCHES HAVING A SILICONIC ADHESIVE MATRIX STABILIZED WITH METHACRYLIC COPOLYMERS

FIELD OF THE INVENTION

The present invention relates to patches suitable for transdermal or topical administration containing adhesive matrices based on storage-stable silicone polymers.

STATE OF THE ART

The therapeutic treatment of patients with pharmaceutically acceptable substances is commonly effected by periodic administration of defined drug doses during the 24 hours of the day. However the classical administration routes such as the oral or injective ones require repeated administration of high dosages to ensure an effective drug level in the body. Controlled drug release by intravenous injection compared with oral administration avoids discontinuous administration and hence the relative release, by maintaining a constant and prolonged drug level, while at the same time avoiding the first stage of hepatic metabolism.

With this in mind, transdermal administration was conceived and developed for systemic medication and local therapy, and presents undoubted advantages not only compared with said traditional systemic applications, but also compared with more conventional topical formulations such as ointments, unguents and creams. In this respect, this latter provides the advantages of controlled direct entry of a drug into the blood circulation associated with indisputable ease of application by the patient. Whether administering a drug by systemic medication or by local treatment, transdermal administration uses the intact skin as the entry portal and the application site for the drug.

Various types of transdermal systems have been conceived and developed.

The first is the reservoir device. In this system the support layer and a membrane able to control the drug release form a drug deposit or reservoir layer which contains the active principle in liquid or gel form. The permeable membrane controls the rate at which the drug is released. As the drug solution is saturated, the release through the membrane is constant with time. An inert permeable film covers either the entire surface in contact with the skin or only a part of the patch depending on the compatibility of the adhesive with the vehicle and the drug

formulation.

The second type of device incorporates a polymer matrix into which the active principle is loaded and within which it has to diffuse through the polymer network from a homogeneous continuous phase or a dispersed phase of the drug in the polymer or as drug microreservoirs uniformly dispersed in the polymer phase. The diffusion rate controls the drug release rate which decreases with time while draining the matrix a part thereof by the part in contact with the skin. As in the case of the reservoir device, adhesion to the skin is provided by an adhesive layer which covers said polymer or alternatively by an adhesive edge.

The third one is the simplest type, in which the adhesive matrix contains the drug and is applied directly onto the skin.

Pressure sensitive adhesives (PSA) play a key role in all three said types of device by ensuring intimate and reliable contact between the transdermal patch and the surface of the skin. In this respect, the patch is flexible and adheres to the skin by applying a slight pressure, without causing irritation, for a time period between 1 and 7 days, without leaving residues once removed. In addition the PSA must be permeable both to the active principles and to the relative absorption enhancers.

The silicone PSAs (III) described in Figure 11 are the condensation products of the polymer (I) shown in Figure 11 which presents silanols as terminal groups, with the silicate resin (II). (I) is a polydimethylsiloxane of low viscosity (12,000-15,000 Cps) or a rubber with silanol functionality in the main chain. The resin (II) is a soluble network of silicates. The ratio resin(II)/polymer(I) in the polycondensate (III) determines the optimum balance between adhesive and cohesive properties. In this respect, on increasing the content of polymer (I), (III) presents higher viscosity and lower resistance to shear, whereas in contrast a high content of resin (II) in (III) produces an adhesive with lower viscosity and higher adhesion.

The silanol residue functionality in (III) can be replaced by a trimethylsiloxane group by means of a trimethylsilylation reaction to give a silicone PSA (IV) as shown in said Figure 11, which hence shows lesser tendency to react further or to form hydrogen bonds with active principles having amino functional groups.

Using this type of technology Dow Corning produces two silicone PSA types: standard Silicone Bio-PSA®, and Silicone Bio-PSA® compatible with amino

groups.

Each of these types is available in 3 different degrees of viscosity, plasticity, and adhesion.

The following Table 1 shows the characteristics of said products.

Table 1

Silicone PSA	Nomenclature	Resin (II)/ polymer(I)	Viscosity (g)*	Adhesion (g/cm)*	Plasticity** (100xcm)
Bio –PSA® Standard	7-4400 (III-a)	65/35	<70	800	64
	7-4500 (III-b)	60/40	70	600	41
	7-4600 (III-c)	55/45	500	400	22
Bio –PSA® Amine-Compatible	7-4100 (IV-a)	65/35	70	750	51
	7-4200 (IV-b)	60/40	150	650	33
	7-4300 (IV-c)	55/45	500	500	26

Said silicone PSAs are available commercially in the form of solutions in solvents chosen from heptane (commercial code 01), ethyl acetate (commercial code 02), toluene (commercial code 03) and typically at concentrations of 60% by weight.

It is recognized that the silicone PSAs are particularly suitable for transdermal systems in that they satisfy said requirements.

Because of their molecular structure, silicone PSAs present the following properties:

low surface energy, low glass transition temperature, high degree of flexibility, good adhesiveness and cohesion force, high permeability to a wide range of therapeutic agents.

Again, in contrast to other acrylic based PSAs and synthetic rubber, they are free of plasticizers, catalysts or other potentially toxic agents.

Silicone PSAs are particularly effective when used to prepare the third aforedescribed type of transdermal patch, i.e. patches in which the active principle is dispersed in the adhesive matrix, in that in addition to said advantages they enable greater diffusion of the active principle in the skin.

However the active principle, present in supersaturation concentrations in these types of adhesive, tends to crystallize with the passage of time, consequently the patch presents lesser therapeutic effectiveness in that the active principle able to diffuse into the skin decreases. This is a serious drawback, as this type of patch cannot be stored other than for very short time periods.

In "Eudragits: Role as crystallization inhibitors in drug in adhesive transdermal system of estradiol" European Journal of Pharmaceutics and Biopharmaceutics 52 (2001) 173-180, P.N. Kotiyan et al. have shown that in a transdermal patch of the third type containing estradiol as active principle and in which the adhesive matrix consists of a hexylacrylate-acrylic acid copolymer, containing 5% of active principle dispersed in the adhesive matrix, particular cationic copolymers of acrylic type in micronized form, specifically Eudragit® E PO and Eudragit® RL PO at concentrations between 0.25-2.0 mg/cm^2 are able to prevent crystal formation even after time periods of 6 months at ambient temperature.

TECHNICAL PROBLEM

The need was felt for a transdermal patch in which the active principle is dispersed within an adhesive matrix consisting of pressure sensitive silicone adhesives (PSAs) which is storage-stable for prolonged time periods.

SUMMARY OF THE INVENTION

The Applicant has now unexpectedly found that storage-stable patches can be obtained by adding between 1 and 10% by weight on the silicone PSA weight of one or more copolymers of acrylic and/or methacrylic esters containing amino or salified ammonium groups.

The Applicant has also found that said acrylic and/or methacrylic ester copolymer quantity range is critical in obtaining the desired results. In this respect, less than 1 wt% concentrations of said component do not prevent the formation of crystals of the active principle. At greater than 10% concentrations of said copolymer, a significant alteration occurs in the mechanical and biopharmaceutical properties.

The present invention therefore provides a patch suitable for transdermal or local administration of at least one active principle comprising:

a) a matrix based on pressure sensitive adhesive silicone polymers containing:

a-1) said active principle in concentrations between 1 and 10% by weight on the total weight of said dry adhesive matrix,

a-2) said silicone polymers in quantities between 80 and 98% by weight on the total weight of said dry adhesive matrix,

a-3) at least one copolymer of cationic type of acrylic and/or methacrylic esters containing amino groups or salified ammonium groups in a concentration between 1 and 10% by weight on the total weight of said adhesive silicone polymers.

b) a support layer on which said adhesive matrix (a) is located,

c) a protective layer disposed on said adhesive matrix.

DESCRIPTION OF THE FIGURES

Figure 1a represents an enlarged (10X) photo taken via a ZEISS AXIOLAB® optical microscope with polarized light, of the patch obtained with the formulation 1 as described in Example 1 at time t=0, Figure 1b represents an enlarged (10X) photo of the same patch after storing for 7 days at 20°C and finally Figure 1c represents an enlarged (10X) photo of the same patch after storing for 28 days at 20°C.

Figure 2a represents an enlarged (10X) photo taken via the same optical microscope with polarized light, of the patch obtained with the formulation 2 described in Example 1 after storing for 7 days at 20°C, Figure 2b represents an enlarged (10X) photo of the patch after storing for 28 days at 20°C.

Figure 3a represents an enlarged (10X) photo taken via the same optical microscope with polarized light, of the patch obtained with the formulation 3 as described in Example 1 at time t=0, Figure 3b represents an enlarged (10X) photo of the same transdermal patch after storing for 30 days at 20°C.

Figure 4a represents an enlarged (10X) photo taken via the same optical microscope with polarized light, of the patch obtained with the formulation 4 at time t=0, Figure 4b represents an enlarged (10X) photo, taken via the same microscope, of the same transdermal patch after storing for 100 days at 20°C.

Figure 5a represents an enlarged (10X) photo taken via the same optical

microscope, of the patch obtained in example 1with the formulation 5 at time t=0, Figure 5b represents an enlarged (10X) photo of the same transdermal patch after storing for 100 days at 20°C.

Figure 6a represents an enlarged (10X) photo taken via the same optical microscope with polarized light, of the patch obtained as described in Example 2 at time t=0, with the formulation 4 at t=0. Figure 6b represents an enlarged (10X) photo of the same transdermal patch after storing for 25 days at 20°C.

Figure 7a represents an enlarged (10X) photo taken via the same optical microscope with polarized light, of the patch obtained as described in Example 2 with the formulation 6 at time t=0, Figure 7b represents an enlarged (10X) photo of the same transdermal patch after storing for 50 days at 20°C.

Figure 8a represents an enlarged (10X) photo taken via the same optical microscope with polarized light, of the patch obtained as described in Example 2 with the formulation 7 after storing for 45 days at 20°C, Figure 8b represents an enlarged (10X) photo of the same transdermal patch after storing for 7 months at 20°C.

Figure 9a represents an enlarged (10X) photo taken via the same optical microscope with polarized light, of the patch obtained as described in Example 2 with the formulation 8 at time t=0, Figure 9b represents an enlarged (10X) photo of the same transdermal patch after storing for 40 days at 20°C.

Figure 10a represents an enlarged (10X) photo taken via the same optical microscope with polarized light, of the patch obtained as described in Example 2 with the formulation 9 after storing for 48 days at 20°C, Figure 10b represents an enlarged (10X) photo of the same transdermal patch after storing for 7 months at 20°C.

Figure 11 represents the synthesis scheme for the silicone PSAs used in the patch of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

The patch of the present invention can contain any type of active principle compatible with and dissolvable in the matrix.

However this system is particularly preferred for drugs with urinary antispastic activity, a particularly preferred drug pertaining to this class being oxybutynin.

Another class of drugs to which this system is applicable are the drugs used to treat benign prostatic hypertrophy, the active principle terazosin and finasteride being particularly preferred.

Another class of active principles usable in the transdermal patch is that of the steroidal hormones and in particular the estrogens such as dehydroepiandrosterone, estradiol, and the progestinics such as norethisterone.

The following classes of drugs applicable to the patch of the present invention can also be mentioned, such as non-steroidal anti-inflammatories and in particular arylalkanoic acids such as ibuprofen, and oxicams such as piroxicam; the non-selective beta blockers such as propanolol, and the selective beta blockers such as atenolol; calcium antagonists and in particular dihydropyridines such as nifedipine; and benzodiazepines such as clonazepam, triazolam, lorazepam.

When the active principle of the present invention contains amino groups, the silicone polymer is preferably chosen from the amine-compatible Bio-PSAs®, 7-4100 (IV-a), 7-4200 (IV-b), 7-4300 (IV-c), the characteristics of which are reported in Table 1. When the active principle does not present amino groups, a standard Bio-PSA® is preferably used chosen from 7-4400 (III-a), 7-4500 (III-b), 7-4600 (III-c).

Other preferred embodiments comprise the use of mixtures of standard Bio-PSA® with amine-compatible Bio-PSA®, both for active principles containing amino groups and for those not containing them.

The patches of the present invention can also contain a mixture of two or three types of 7-4400 - 7-4600 standard Bio-PSA® polymers or a mixture of two or three types of 7-4100 - 7-4300 amine-compatible Bio-PSA® polymers.

The expert of the art can therefore, on the basis of the type of active principle and the mechanical properties to be obtained, choose which silicone polymers or whether to opt for a mixture of silicone polymers chosen from the aforementioned.

According to a preferred embodiment, use is made of solutions of said silicone PSAs in ethyl acetate or commercial products containing 60% of polymer (i.e. the commercial standard Bio-PSA® products 7-4402, 7-4502, 7-4602, and the amine-compatible products 7-4102, 7-4202, 7-4302).

The copolymer (a-3) is preferably chosen from:

i) copolymers of cationic type based on dialkylaminoalkylmethacrylate, and neutral alkylmethacrylate esters, where alkyl means a C_1-C_{10} linear or branched alkyl residue, said copolymers having an average molecular weight between 100,000 and 500,000 and in which the ratio of repetitive dialkylaminoalkylmethacrylate/neutral ester units is between 2:1 and 1:2;

ii) copolymers of cationic type based on trialkylammoniumalkylmethacrylate, and neutral alkylmethacrylate esters, neutral alkylacrylate esters, where alkyl means a C_1-C_{10} linear or branched alkyl residue, said copolymers having an average molecular weight between 100,000 and 500,000 and in which the alkylmethacrylate and methylmethacrylate/trialkylammoniumalkylmethacrylate ratio is between 40:1 and 20:1;

iii) mixtures of the copolymers (i) and (ii).

According to a particularly preferred embodiment the copolymer is chosen from the group consisting of:

a-3-1) poly-(butylmethacrylate), (2-dimethylaminoethyl)-methacrylate, methylmethacrylate) in which the ratio of said 3 monomers is respectively 1:2:1, and is characterised by an average molecular weight of 150,000. This product is available commercially with the brand name of Eudragit® E100,

a-3-2) poly(ethylacrylate, methylmethacrylate, trimethylammoniumethylmethacrylate chloride) characterised by an average molecular weight of 150,000 and in which the ratio of said monomers is 1:2:0.2. This product is available commercially with the brand name of Eudragit® RL100,

a-3-3) poly(ethylacrylate, methylmethacrylate, trimethylammoniumethylmethacrylate chloride) characterised by an average molecular weight of 150,000 and in which the ratio of said monomers is 1:2:0.1. This product is available commercially with the brand name of Eudragit® RS100,

a-3-4) mixtures of two or all the copolymers a-3-1), a-3-2), a-3-3).

Said copolymers are preferably added during the preparation of the adhesive patch matrix in the form of an ethyl acetate solution which contains them in a quantity of about 10%.

The acrylic copolymer (a-3-1) can be used when the adhesive matrix contains either an active principle of basic type or an active principle of acid, alcohol or

other type.

Eudragit RS100 (a-3-3) is preferably used when the active principle is of basic type, and Eudragit RL100 (a-3-2) when the active principle is of acid type.

The adhesive matrix can contain other additives such as solubilizing agents, for example polypropylene glycol, polyethylene glycols of various molecular weights, glycerol, and absorption enhancers such as caprolactone, unsaturated fatty acids and their esters, and terpenes.

The support layer can be chosen from any one of those habitually used for transdermal patches. If necessary a film permeable to water vapour can be used to prevent maceration of the skin, such as that available commercially with the brand name Cotran® 97.15 from 3M.

The protective film (c) used must be a non-siliconized film such as that available commercially with the brand name Scotch Pack® 1022 from 3M.

The patches of the present invention are prepared by a process comprising the following stages:

α) adding the solution of polymer of acrylic and/or methacrylic esters of cationic type containing amino groups or salified ammonium groups (a3) in an organic solvent, preferably ethyl acetate, to the solution of silicone PSA in the same organic solvent used for (a3), preferably ethyl acetate,

β) adding the active principle to the mixture obtained in the preceding stage (α), and keeping the resultant mixture under stirring for 3 hours,

γ) spreading on the support (b) the mixture coming from the preceding stage (β), drying it and applying the protective sheet (c) with conventional machines.

Some examples of the preparation of the patch of the present invention are provided for illustrative but not limitative purposes.

EXAMPLE 1

1-A Preparation of the polymer solutions used for preparing the matrix

Composition:

Form. no	Oxybutynin base (g)	BIO-PSA 7-4302	BIO-PSA 7-4202 (g)	Propylene glycol (g)	Eu. E* (g)	Eu. RL* (g)	Eu. RS* (g)	Prep. date

		(g)						
1	2.58	97.42	-	-	-	-	-	05/07/01
2	2.35	88.61	-	2.98	6.06	-	-	05/07/01
3	2.10	79.10	-	2.66	16.14	-	-	11/06/01
4	1.83	81.53	-	-	16.64	-	-	28/09/01
5	1.83	81.53	-	-	-	-	16.64	28/09/01
6	1.83	81.53	-	-	-	16.64	-	28/09/01
7	1.57	69.90	-	-	28.53	-	-	01/10/01
8	1.57	69.90	-	-	-	-	28.53	01/10/01
9	1.75	77.96	-	-	20.29	-	-	03/10/01
10	1.75	77.96	-	-	-	-	20.29	03/10/01
11	1.65	73.57	-	-	24.77	-	-	03/10/01
12	1.65	73.57	-	-	-	-	24.77	03/10/01
13	2.44	-	97.56					28/05/01
14	2.20	-	81.50				16.30	11/06/01
15	2.10	-	79.10	2.66			16.14	11/06/01
16	2.10	-	79.10	2.66	16.14			11/06/01
17	3.59	64.90	28.34				3.17	30/11/01

*Polymer solution of Eudragit E 100, RL 100 or RS 100 10% m/m in ethyl acetate

The formulations were prepared by adding the Eudragit® solution and, if necessary, the propylene glycol to the Bio-PSA 7-4302 maintained under stirring. The oxybutynin was added to the mixture obtained, maintaining the system under stirring for 3 hours.

The polymer system obtained was left to under rest until complete removal of air, before being used.

1-B Patch preparation

Support: Cotran® 97.15 (3M);

Protective sheet: Scotchpack® 1022 (3M)

The matrix was spread on the protective sheet and dried using the Matis spreading machine, model LTE-S (M).

Spreading rate	1 m/min;

Drying time	20 min;
Drying temperature	50° C
Distance blade-protective sheet	350 μm

On termination of the process the patch obtained was packaged in air-impermeable envelopes and stored at 20°C.

1-C Oxybutynin content

The oxybutynin content was determined by dissolving a 2.54 cm^2 sample in a suitable volume of ethyl acetate and determining the content by HPLC-UV.

1-D Monitoring of crystal formation

Formation of oxybutynin crystals was monitored on a 144 cm^2 surface by optical microscope. The patches were checked immediately after preparation and then once a week. Any matrix changes were recorded by photographing with 10x magnification a patch sample made to adhere to a glass slide.

1-E Study of cutaneous permeability

The in vitro permeability studies were conducted by the modified Franz-type diffusion cell method (P. Minghetti, J. Pharm. and Pharmacol., 51(6): 729-734, 1999), using as membrane human epidermis from one and the same donor. The oxybutynin quantity which had permeated was determined by HPLC-UV. The results are the mean of three determinations.

1-F Adhesiveness

The capacity of the patches to adhere to the skin was evaluated by the Thumb Tack Test (D. Satas "Tack" in Handbook of Pressure Sensitive Technology edited by Donatas Satas, 1999: Minghetti et al. Drug Dev. Ind. Pharm., 25(1): 1-6, 1999).

1-G Results

Monitoring of crystal formation

Oxybutynin recrystallization time

Form.	Days
1	7
2	19
3	45
4	>360
5	>360

6	24
7	>360
8	>360
9	>360
10	>360
11	>360
12	>360
13	90
14	180
15	150
16	150
17	>360

1-H Oxybutynin content and cutaneous permeability

Oxybutynin content in the patches and quantity permeated in 24 h

Form.	Content ($\mu g/cm^2$)	quantity permeated in 24h ($\mu g/cm^2$)
4	355 ± 14	120.01 ± 20.71
5	329 ± 21	110.38 ± 23.12
6	381 ± 9	90.01 ± 28.38
12	368 ± 15	103.89 ± 39.24

EXAMPLE 2

2-A Preparation of the polymer solutions used for preparing the matrix

Composition:

Form. No.	Ibu (g)	Bio-psa 4202 (g)	Bio-psa 4302 (g)	Bio-psa 4502 (g)	Bio-psa 4602 (g)	Prop. glycol	Eu E* (g)	Eu RS* (g)	Eu RL* (g)	Prep. date.
1	1.96	98.04	-	-	-	-	-	-	-	06/03/01
2	1.96	-	98.04	-	-	-	-	-	-	24/01/01
3	1.96	-	-	98.04	-	-	-	-	-	06/03/01

4	1.96	-	-	-	98.04	-	-	-	-	06/03/01
5	1.91	-	95.69	-	-	2.39	-	-	-	01/03/01
6	1.91	-	-	-	95.69	2.39	-	-	-	10/04/01
7	1.63	-	-	-	81.63	2.04	14.69	-	-	14/06/01
8	1.63	-	-	-	81.63	2.04	-	14.69	-	14/06/01
9	1.63	-	-	-	81.63	2.04	-	-	14.69	13/06/01

*Polymer solution of Eudragit E 100, RL 100 or RS 100 10% m/m in ethyl acetate

The formulations were prepared by adding the Eudragit® solution and, if necessary, the propylene glycol to the appropriate BIO PSA maintained under stirring.

The ibuprofen was added to the mixture obtained, maintaining the system under stirring for 3 hours.

The polymer system obtained was left under rest until complete removal of air, before being used.

2-B Patch preparation

Support: Schochpak 1022 (3M);

Protective sheet: Scotchpack 1022 (3M)

The matrix was spread on the protective sheet and dried using the Matis spreading machine, model LTE-S (M).

Spreading rate	1 m/min;
Drying time	20 min;
Drying temperature	50° C
Distance spreader blade-protective sheet	300 μm

On termination of the process the patch obtained was packaged in air-impermeable envelopes and stored at 4°C and 20°C.

2-C Ibuprofen content

The ibuprofen content was determined by dissolving a 2.54 cm^2 sample in a suitable volume of ethyl acetate and determining the content by HPLC-UV.

2-D Monitoring of crystal formation

Formation of ibuprofen crystals was monitored on a 144 cm^2 surface by optical microscope. The patches were checked immediately after preparation and then

once a week. Any matrix changes were recorded by photographing with 10x magnification a patch sample made to adhere to a glass slide.

2-E Study of cutaneous permeability

The in vitro permeability studies were conducted by the modified Franz-type diffusion cell method (P. Minghetti, J. Pharm. and Pharmacol., 51(6): 729-734, 1999), using human epidermis as membrane from one and the same donor. The ibuprofen quantity which had permeated was determined by HPLC-UV. The results are the mean of three determinations.

2-F Adhesiveness

The capacity of the patches to adhere to the skin was evaluated by the Thumb Tack Test (D. Satas "Tack" in Handbook of Pressure Sensitive Technology edited by Donatas Satas, 1999: Minghetti et al. Drug Dev. Ind. Pharm., 25(1): 1-6, 1999).

2-G Results

Ibuprofen content e quantity permeated in 24 h

Form.	Content ($\mu g/cm^2$)	quantity permeated in 24h ($\mu g/cm^2$)
6	368± 15	109 ± 13
7	323± 23	117± 4
9	338± 10	145 ± 25

Days before appearance of crystals

Form.	Temperature	Days
1	20°C	1
2	20°C	5
3	20°C	25
4	20°C	25
5	20°C	5
6	20°C	50
7	20°C	> 21 months
7	4°C	> 21 months
7	40°C	> 12 months

8	20°C	40
9	20°C	> 21 months
9	4°C	> 21 months
9	40°C	> 12 months

EXAMPLE 3

Patches containing nifedipine (NIF)

3-A Preparation of the polymer solutions used for preparing the matrix

Composition:

Form. No.	NIF (g)	Bio-psa 4202 (g)	Bio-psa 4302 (g)	Eu E* (g)	Eu RL* (g)	Eu RS* (g)	Prep. Date
1	1.96	98.04					06/03/2002
2	1.64	81.97		16.39			06/03/2002
3	1.64	81.97			16.39		06/03/2002
4	1.64	81.97				16.39	06/03/2002

*Polymer solution of Eudragit E 100, RL 100 or RS 100 10% m/m in acetone

The formulations were prepared by dissolving nifedipine in the Eudragit solution and adding the solution obtained to the appropriate BIO PSA maintained under stirring. The mixture obtained was maintained under stirring for 3 hours. The polymer system obtained was left under rest until complete removal of air, before being used.

3-B Patch preparation

Support: Schochpak 1022 (3M);

Protective sheet: Scotchpack 1022 (3M)

The matrix was spread on the protective sheet and dried using the Matis spreading machine, model LTE-S (M).

Spreading rate	1 m/min;
Drying time	20 min;
Drying temperature	50° C
Distance blade-protective sheet	350 μm

On termination of the process the patch obtained was packaged in air-

impermeable envelopes and stored at 4°C and 20°C.

3-D Monitoring of crystal formation

Formation of nifedipine crystals was monitored on a 144 cm^2 surface by optical microscope. The patches were checked immediately after preparation and then once a week. Any matrix changes were recorded by photographing with 10x magnification a patch sample made to adhere to a glass slide.

3-E Results

Days before appearance of crystals

Form.	Temperature	Days
1	20°C	7
2	20°C	>10 months
3	20°C	>10 months
4	20°C	>10 months

EXAMPLE 4

Patches containing dehydroepiandrosterone (DHEA)

4-A Preparation of the polymer solutions used for preparing the matrix

Composition:

Form. no.	DHEA (g)	Bio-psa 4602 (g)	isopropanol	Eu E (g)	Eu RL (g)	Eu RS (g)	Prep date
1	1.67	81.67	16.66	-	-	-	28/01/2002
2	1.64	81.97	-	-	-	16.39*	13/12/2001
3	1.64	81.97	-	16.39*	-	-	13/12/2001
4	2.04	81.63	-	16.33**	-	-	28/01/2002
5	1.43	71.43	12.85	-	14.29*	-	25/02/2002
6	1.43	71.43	12.85	-	-	14.29*	25/02/2002

*Polymer solution of Eudragit E 100, RL 100 or RS 100 10% m/m in ethyl acetate

**Polymer solution of Eudragit E 100 in isopropanol

Formulation No. 1 was prepared by dissolving the DHEA in isopropanol and adding the solution obtained to the BIO PSA 4602 maintained under stirring. The system obtained was maintained under stirring for 3 hours.

Formulation No. 2 was prepared by dispersing the DHEA in the BIO-PSA and

adding the Eudragit solution. The system obtained was maintained under stirring for 3 hours.

Formulations Nos. 3, 4 were prepared by dissolving the DHEA in the Eudragit solution and adding the solution obtained to the BIO PSA 4602 maintained under stirring. The mixture obtained was maintained under stirring for 3 hours.

Formulations Nos. 5, 6 were prepared by dissolving the DHEA in isopropanol. The final polymer system was obtained by adding the solution obtained to that of Eudragit in the BIO-PSA. The mixture obtained was maintained under stirring for 3 hours.

All the polymer systems obtained were left under rest until complete removal of air, before being used.

4-B Patch preparation

Support: Schochpak 1022 (3M);

Protective sheet: Scotchpack 1022 (3M)

The matrix was spread on the protective sheet and dried using the Matis spreading machine, model LTE-S (M).

Spreading rate	1 m/min;
Drying time	15 min;
Drying temperature	50° C
Distance blade-protective sheet	350 μm

On termination of the process the patch obtained was packaged in air-impermeable envelopes and stored at 4°C and 20°C.

4-C Monitoring of crystal formation

Formation of dehydroepiandrosterone crystals was monitored on a 144 cm^2 surface by optical microscope. The patches were checked immediately after preparation and then once a week. Any matrix changes were recorded by photographing with 10x magnification a patch sample made to adhere to a glass slide.

4-D Results

Days before appearance of crystals

Form.	Temperature	Days
1	20°C	7

2	20°C	>1 year
3	20°C	>1 year
4	20°C	>1 year
5	20°C	>10 months
6	20°C	>10 months

EXAMPLE 5

Percutaneous absorption of patches containing oxybutynin after single and multiple dose in healthy male volunteers

The object of this pilot study is to evaluate the in vivo absorption, kinetic profile and adhesiveness of the 36 cm^2 patch containing oxybutynin based on formulations No. 17 (patch A), No. 8 (patch B) and No. 14 (patch C) of the example.

Method

Single and multiple application, pharmacokinetic pilot studies on the same subject in three successive phases.

Number of subjects (programmed and analyzed)

Three subjects programmed, three subjects analyzed.

Inclusion criteria

Sex: males, aged 18-45 years, good healthy state, no allergic form, low alcohol, tobacco and caffeine consumption.

Duration of treatment

Phase I and II single dose, phase III three applications for 3 days

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ANOVA	analysis of variance
AUC_t	area below concentration/time curve
C_{max}	maximum plasma concentration
CV	variance coefficient
T_{max}	time for attaining C_{max}
$t_{1/2}$	half life
C_{ssmax}	maximum concentration in the steady state
t_{ssmax}	time for attaining maximum concentration in the steady state
AUC_{ss}	area under steady state concentration/time curve

C_{mean} mean concentration

C_{ssmin} minimum concentration in the steady state

EVALUATION CRITERIA (KINETIC)

In order to evaluate the pharmacokinetic profile of the three formulations, a blood sample was taken before application and after 1, 2, 4, 6, 8, 10, 12, 16, 24, 28, 30, 32, 36, 40 and 48 hours for patches A and B. In the case of patch C the sample was taken before application and after 1, 2, 4, 6, 8, 10, 12, 16, 24, 28, 30, 32, 36, 40, 48, 50, 52, 54, 56, 60, 64, 72 hours. The oxybutynin and its main metabolite desethyloxybutynin were determined in plasma. The main kinetic parameters measured and/or calculated were: C_{max}, t_{max}, AUC_t for formulations A and B; C_{ssmax}, t_{ssmax}, AUC_{ss} and C_{mean} for formulation C.

Statistical methods

The data and the measured parameters are described using classical statistics: mean, SD, CV%, minimum and maximum values.

The calculated values of AUC_{0-24h} and C_{max} in plasma for oxybutynin and desethyloxybutynin after administering the patches A, B and C were compared by variance analysis (ANOVA) with a significance level $p < 0.05$.

Results

Formulation A

The concentration peaks were: $t_{max} = 23.33 \pm 13.01$, $C_{max} = 0.47 \pm 0.20$ ng/mL. The half life was 24.15 ± 20.90 h and MRT 44.74 ± 28.46 h, the AUC_t was 20.76 ± 0.78 ng*h/mL.

Formulation B

The concentration peaks ($C_{max} = 0.69 \pm 0.29$ ng/mL) were attained after 20 ± 6.93 h, the AUC_t was 16.57 ± 5.70 ng*h/mL, half life 15.40 ± 5.40 h and MRT 33.07 ± 4.34 h.

Formulation C

In the steady state C_{ssmin} was 0.30 ± 0.17 ng/mL and C_{ssmax} 0.61 ± 0.27 with C_{mean} 0.48 ± 0.22 ng/mL and 69.72 ± 11.96 as %PTF. The AUC_{ss} was 11.42 ± 5.33 ng*h/mL.

To compare the three formulation studies, the Shapiro-Wilk test for normal distribution was carried out for C_{max} ($p = 0.976$) and for AUC_{0-24h} ($p = 0.711$),

indicating no statistical difference between them.

The variance analysis was carried out using ANOVA, and provided the same results: for C_{max} ($p = 0.104$) and for AUC_{0-24h} ($p = 0.082$).

Conclusions

The patches A, B and C reached satisfactory plasma concentrations of oxybutynin and desethyloxybutynin within the 0-24 hour application range. Absorption seems qualitatively to be fairly rapid and protracted, so ensuring pharmacological activity with a single daily application.